> Wahlig teaches compositions consisting of a drug delivery system comprising collagen, which is resorbable by the body. Wahlig teaches collagen in lyophilized form, with a delay release of active materials. See column 3, lines 11-03 and column 2, lines 36-67. Wahlig teaches collagen having spheroidal shaped bodies of various dimensions, for example, spheroids with a diameter of 0.5-10mm, and granulates with a diameter of 0.1-5 mm. Wahlig also teaches that he composition can also be formed into a powder. See column2, lines 63-68, bridging column 3, lines 1-10. Wahlig teaches the active materials consists of antibiotics such as two or more aminoglycoside antibiotics which include gentamycin and clindamycin. See column 5, lines 8-40. In addition, Wahlig teaches calcium phosphate and tricalcium phosphate. Se column 6, lines 1-9. The reference clearly teaches resorbable collagen in lyophilized form with a delayed release of active materials.

Applicant respectfully traverses this rejection. The reference of record does not teach each and every element of the presently claimed invention and thus does not anticipate the present claims.

The test for anticipation is whether each and every element as set forth is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987); MPEP §2131. The identical invention must be shown in as complete detail as is contained in the claim. *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989); MPEP §2131. The elements must also be arranged as required by the claim. *In re Bond*, 15 USPQ2d 1566 (Fed. Cir. 1990).

The presently pending claims are drawn to an active ingredient matrix in the form of a biologically resorbable, porous nonwoven of collagen fibrils in lyophilized form with a retarded release of active ingredients.

In contrast, the Wahlig reference teaches a shaped mass resorbable in the body, which comprises collagen and a bioresorbable binding agent for collagen. The Wahlig reference teaches a collagen product that includes a polymer based binding agent for the collagen. This is in contrast to the presently claimed lyophilized collagen fibril matrix that does not require such additives.

Further, the Wahlig reference teaches away from the presently claimed lyophilized collagen fibril matrix. The Examiner's attention is drawn to column 3, lines 12-17 of the Wahlig reference which states the following: "Whereas liberation from conventional (e.g. lyophilized) collagen takes place relatively quickly, the active material can be liberated protractedly from the composition of this invention, i.e. over a desired period of time, in the necessary concentrations." Thus, Wahlig teaches that release of an active ingredient from lyophilized collagen occurs "relatively quickly", whereas the present claims are drawn to a lyophilized collagen "with a retarded release of active ingredients".

Further, all of the active agents mentioned in the Wahlig

reference have good solubility in water, which is not the case with the present invention. For example, the clindamycin used by Wahlig (good solubility in water) is a different component than the clindamycin-palmitate (which is a palmitic acid ester derivative of clindamycin) used in the present invention, which has poor solubility in water.

Thus, the retarded release of the Wahlig product is related to its particular composition and structure obtained in a specific procedure involving the heating up to 200 C and pressurizing up to 1200 bar, which is in contrast to the procedure employed to prepare the active ingredient matrix according to the presently pending claims.

Accordingly, each and every element of the presently pending claims are not disclosed in the Wahlig reference as required by *Verdegaal Bros. v. Union Oil Co. of California*. Thus, the Wahlig reference fails to anticipate these claims.

Accordingly, applicant respectfully requests that the Examiner reconsider and withdraw the present rejection of claims 22-30.

2. Rejection of claims 22-28 and 30-55 under 35 U.S.C. §102(b)

The Official Action states that claims 22-28 and 30-55 have been rejected under 35 U.S.C. §102(b) as being anticipated by Chu (U.S. Patent No. 5,219,576) for the following reasons:

Chu teaches collagen wound healing matrices and a method for making biodegradable collagen implants, formed of collagen fibrils that are not chemically cross-linked, having a bulk density of 0.01 to 0.3 g/cm3 and having at least about 80% of pores which normally has a pore size of 35 to 250 microns in diameter. Chu further discloses that the wound healing matrix serves as an effective sustained delivery system for bioactive agent. See abstract and column 6, line 68, bridging column 7, lines 1-10.
Chu discloses a method for making collagen implants by providing an acidic aqueous solution of collagen, precipitating the collagen from the solution, and forming a homogeneous dispersion of the precipitated collagen fibrils, casting the dispersion in a mold to a desired thickness, flash-freezing the cast dispersion at a temperature below about -20 degrees C; and lyophilizing the frozen cast dispersion to form a collagen implant. Bioactive additives can be added to the homogeneous dispersion before or after the pH of the solution has been adjusted. See column 2, lines 18-36. Chu teaches that glycosaminoglycans, bioactive and/or non-bioactive agents are added to the collagen dispersion prior to flash freezingand lyophilization. See column 5, lines 15-18. Adding heparin to the dispersion has been found to affect the pore size of the implant. See column 6, lines 52-58. Chu also teaches that the fibrous implants are about 2 to about 8 mm thick and that the implants may easily be cut to shape in order to fill the wound closely. See column 7, lines 15-30.

Applicant respectfully traverses this rejection. The reference of record does not teach each and every element of the presently claimed invention and thus does not anticipate the present claims.

The presently pending claims are drawn to an active ingredient matrix in the form of a biologically resorbable, porous nonwoven of collagen fibrils in lyophilized form with a retarded release of

active ingredients, containing at least one homogeneously distributed active ingredient poorly soluble in water and body fluids and having a physiological medium solubility of < 10 mg/ml.

In contrast, the Chu reference, while related generally to collagen implants that are useful as wound healing matrices, does not address the problems related to active ingredients that are poorly soluble in water and body fluids. At the very least, the Examiner has failed to meet her procedural burden to provide a teaching related to this claim limitation.

Further, collagen fibrils in suspension are used to prepare the active ingredient matrix of the presently pending claims. The inventive fibrils are obtained directly from animal skin by swelling, not dissolving. In contrast, the collagen implants of Chu are prepared from acidic aqueous solutions of collagen. In addition, the natural fibrils according to the present invention differ from the synthetic fibrils obtained after dissolving and reprecipitating collagen as taught by Chu.

Accordingly, each and every element of the presently pending claims are not disclosed in the Chu reference as required by *Verdegaal Bros. v. Union Oil Co. of California.* Thus, the Chu reference fails to anticipate these claims.

Accordingly, applicant respectfully requests that the Examiner reconsider and withdraw the present rejection of claims 22-28 and

30-55.

3. Rejection of claims 22, 31-55 under 35 U.S.C. §103(a)

The Official Action states that claims 22 and 31-55 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Wallace et al. (U.S. Patent No. 4,789,663) in view of JP 41007119A. The Official Action states the following in relevant part:

> Wallace teaches methods of repairing bone defects or reconstructing a matrix for new bone growth, by implanting in the defect, purified reconstituted fibrillar collagen (Type 1), which may be in lyophilized form. Wallace teaches a method for preparing lyophilized collagen gel. Wallace also teaches a method for preparing bone collagen powder. Wallace does not particularly teach an active ingredient.
> However, the Japanese reference teaches a collagen sponge containing silver sulfadiazine.
> It would have been obvious to one of ordinary skill at the time the invention was made to use the composition taught by Wallace, because Wallace teaches methods of repairing bone defects by implanting purified, reconstituted fibrillar collagen, which may be in lyophilized form. The use of an active ingredient in the composition taught by the Japanese reference would have been obvious to one of ordinary skill in the art because the Japanese reference teaches a composition which is useful for the purpose of incorporating silver sulfadiazine in a collagen sponge matrix. The expected result would be a collagen sponge matrix which may be in lyophilized form, containing an active ingredient which is poorly soluble in water.

Applicants respectfully traverse the rejection of claims 22 and 31-55. The reference of record does not teach or suggest applicants' inventive subject matter as a whole as recited in the

claims. The Examiner has failed to establish a *prima facie* case of obviousness against the presently rejected claims.

To establish a *prima facie* case of obviousness, the PTO must satisfy three requirements. First, the prior art relied upon, coupled with the knowledge generally available in the art at the time of the invention, must contain some suggestion or incentive that would have motivated the skilled artisan to modify a reference. *In re Fine*, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988). Second, the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen Inc. v. Chugai Pharm. Co.*, 18 USPQ2d 1016, 1023 (Fed. Cir. 1991). Lastly, the prior art references must teach or suggest all the limitations of the claims. *In re Wilson*, 165 USPQ 494, 496 (C.C.P.A. 1970).

First, as conceded by the Examiner, the Wallace reference fails to disclose an active ingredient. Further, the collagen fibrils of the present invention are natural lyophilized collagen fibrils. In contrast, Wallace teaches bone defect repair based on reconstituted fibrillar skin collagen or bone collagen powder. Further, the process for preparing the lyophilized collagen fibrils of the present invention is completely different from the manner in which the reconstituted collagen of Wallace is prepared.

Japanese patent JP 410071199 to Morita does not remedy these deficiencies. Morita teaches a sulfadiazine silver doped collagen product for use as artificial skin, prepared from a collagen solution. Morita uses dissolved collagen for this purpose. Morita also teaches thermal treatment and chemical cross-linking of the collagen matrix, a processing scheme which contrasts with the process by which the presently claimed matrix is prepared.

Accordingly, the prior art references fail to fairly teach each and every element of the present claims as required by *In re Wilson*.

Accordingly, applicant respectfully requests that the Examiner reconsider and withdraw the present rejection of claims 22 and 31-55.

CONCLUSION

Based on the above arguments, applicant believes that the presently pending claims are patentable over the prior art of record. Accordingly, applicant respectfully requests that the Examiner reconsider and withdraw the rejection of claims 22-55 and allow all claims to proceed to grant.

If the Examiner has any questions or wishes to discuss this matter, she is welcomed to contact the undersigned attorney.

Respectfully submitted,

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